REMARKS

Claims 28, 41 and 75-110 are pending and under consideration. Of these, claims 78, 79, 81, 85, 86, 92, 95-96, 101, 102, 104, 108 and 109 are withdrawn from consideration. With this Amendment, claims 28, 41, 78, 79, 82, 83, 93, 97, 101, 102, 105 and 106 are amended. Claims 94 and 110 are canceled. Thus, after entry of this Amendment, claims 28, 41, 75-93 and 95 to 109 are pending and under consideration. The amendments of the claims and the various objections and rejections raised in the Office Action are discussed in more detail, below. Because the amendments set forth above are submitted to put the application in better condition for allowance or appeal, it is believe that the amendment should be entered despite being requested after final rejection.

All amendments and cancellations are made without prejudice or disclaimer. Applicants explicitly retain the right to pursue any deleted subject matter in one or more continuation applications. No new matter is believed to have been added by any of the amendments.

Information Disclosure Statement

The Examiner is thanked for return of the various PTO Form 1449s for the Information Disclosure Statements so far considered.

Regarding the comment on reference **CCR** at page 2 of the Office Action dated Aug. 17, 2007, said reference is Kovacs (Fourth International Electronic Conference on Synthetic Organic Chemistry (ECSOC-4), **www.mdpi.org/ecsoc-4htm**, September 2000) as identified on page 5 of the present Office Action.

Applicants further note that in parent application USSN 10/655,731, the Office made reference to the European Search report and commented that it had not reviewed the claims in that case. For convenience of the Examiner, a copy of the presently pending claims in the European counterpart application is attached as **Exhibit D** and a copy of the presently pending Office Action in said counterpart European application is attached as **Exhibit E**.

Objection(s) to the Abstract

The abstract of the specification was objected to under 37 C.F.R. §1.72. It is submitted that this objection is overcome by the present amendment(s).

Amendment to the Specification

A request to amend the section of the present specification entitled: "*Cross Reference To Related Applications*" is presented. The current application is properly a 'divisional' application of USSN 10/655,731 (the 'parent application') because in both this application and the parent application essentially identical restriction requirements where issued on 07/09/2006 and 06/09/2006, respectively, which identified Group I, claims 1-27, as being directed to a first invention, Group II, claims 28-51, as being directed to a second invention and Group III, claims 52-74, as being directed to a third invention. In the parent application, the invention associated with Group I claims was elected for prosecution. In the present application, the invention associated with Group II claims was elected for prosecution.

Rejections under 35 USC § 112, First Paragraph

Claims 28, 75-77, 80, 82-84, 97-100, 103, 105-107 and 110 were rejected for allegedly introducing new matter. Independent claims 28 and 97 are amended and claim 110 is canceled. It is respectfully submitted that the rejections are moot in light of the currently pending claims. Withdrawal of the rejection is respectfully requested.

Rejections under 35 USC § 112, Second Paragraph

Claim 110 was rejected as allegedly being indefinite due to alleged deficiencies. Claim 110 is canceled. It is respectfully submitted that this rejection is moot in light of the currently pending claims. Withdrawal of the rejection is respectfully requested.

Rejections Under 35 USC§ 103(a)

I Rejection over Breipohl, Kovacs, Thomson and Koch

a) Claims 28, 75-86 and 97-109

At pages 4-5 of the Office Action, claims 28, 41, 75-77, 80, 82-84, 87-90, 93, 97-100, 103, 105-107 and 110 stand rejected under 35 U.S.C. §103(a) as unpatentable over Breipohl (US Pat. No. 6,121,418) in view of Kovacs (Fourth International Electronic Conference on Synthetic Organic Chemistry (ECSOC-4), **www.mdpi.org/ecsoc-4htm**, September 2000), Thomson (*Tetrahedron Letters*, **51:** 6179-6194 (1995) and Koch (*J. Peptide Res.*, **49:** 80-88 (1997)). This rejection is respectfully traversed.

Applicants refer to and reiterate their arguments at pages 13-19 of the response dated April 19, 2007. With respect to independent claims 28 and 97, Applicants specifically maintain that none of Breipohl, Kovacs, Thomson and/or Koch teaches the element/limitation of "*treating the solid support for a period of no more than about 1 to about 2 minutes with a deprotection reagent, under basic conditions, that deprotects the base-labile N-terminal amine protecting group*". Applicants further assert that these references fail to teach any specific protocol whatsoever for the removal of the '*base-labile N-terminal amine protecting group'* group of a PNA monomer (or oligomers in general) cleavable linked to a sterically-hindered acid-forming cleavable linker that forms a PNA oligomer comprising a C-terminal acid when the assembled PNA oligomer is cleaved from the support.

The limitation "*no more than*" has been introduced into claims 28 and 97 to address the concern articulated at page 8 of the present Office Action which asserts that by use of the open ended transition word "comprising", the phrase "*about 1 to about 2 minutes*" in former claims 28 and 97 read on a treatment of 10 minutes. The amendment to claims 28 and 97 is supported by the specification as filed and, for example, by Example 1.

By its reliance on *Syngenta Seeds, Inc. v. Monsanto*, the Office appears to implicitly acknowledge that Breipohl, Kovacs, Thomson and/or Koch fail to expressly teach the element of "*treating the solid support for a period of no more than about 1 to about 2 minutes with a deprotection reagent, under basic conditions, that deprotects the base-labile N-terminal amine protecting group*" since the conclusion of the argument is that: "*... the limitation of "1-2 minutes" is an obvious variation of the times taught by Kovacs and/or Koch, and is considered routine experimentation.*" (OA at page 11) This analysis is flawed for several reasons.

In the present case, the ordinary practitioner must consider the effects of competing reactions when deciding the conditions (e.g. time and nature of the "deprotection reagent") to apply to remove the "*base-labile N-terminal amine protecting group*" (see claims 28 and 97). As has been argued (Applicants' submission dated April 19, 2007 at pages 16-17), although PNA was long-known to be prone to base-catalyzed decomposition, the ordinary practitioner must balance the need to apply conditions strong enough to remove the "*base-labile N-terminal amine protecting group*" (e.g. the Fmoc group - which must be removed from the first PNA monomer before the second PNA monomer can be reacted (coupled) to form the PNA dimer) against the effects of base-catalyzed decomposition (e.g. cyclization and elimination of the first PNA

monomer from the support which leads to very low loading). No similar conflicting experimental parameters were present in *Syngenta*. Moreover, none of Breipohl, Kovacs, Thomson and/or Koch provides insight into whether or not a 1-2 minute deprotection step is sufficient to remove the "*base-labile N-terminal amine protecting group*", such as Fmoc.

Second, independent claims 28 and 97 are directed to methods with employ acid-forming cleavable linkers (i.e. linkers that produce C-terminal acids) and not linkers that form PNAs comprising C-terminal amides. A review of Breipohl, Kovacs, Thomson and Koch reveals that not a single one of these references provides a specific protocol for deprotecting the Fmoc group from a PNA oligomer linked to an acid-forming cleavable linker. Thus, these references are devoid of representative teachings that would give rise to a reasonable expectation of success.

Third, although at least Kovacs and Thomson (Breipohl and Koch appear to be silent to the amount of time needed to deprotect the N-terminal Fmoc group) were aware of the problem of base-catalyzed decomposition of PNA, they selected conditions which required at least 10 minutes (total) of treatment with a deprotection reagent (e.g. 20% piperidine in DMF) for the removal of the base-labile N-terminal protecting group (i.e. Fmoc). As argued by Applicants[1], this fact alone suggests that treatment of 1-2 minutes with the deprotection reagent for the removal of the base-labile N-terminal protecting group was likely **not even** 'obvious to try' because neither Kovacs nor Koch, who were reporting on **optimized PNA synthesis protocols** (Kovacs - title and abstract use the word "optimization"; Koch[2], first sentence of the abstract "*An optimized automated PNA synthesis protocol is reported*"), describe anything close to using a 1-2 minute deprotection cycle for removal of the "*base-labile N-terminal amine protecting group*".

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1 At page 5, the present Office Action asserts: "*Applicants are also of the opinion that the rejection [sic] based on such references amounts to an 'obvious to try' approach.*" Respectfully, Applicants' remarks at page 17 of the submission dated April 19, 2007 argued that: "*In fact, that Thomson and Kovacs didn't modify the deprotection conditions in the manner asserted as being obvious, suggests that this approach may not have even been "obvious to try"...*".

2 As has been argued by Applicants, Koch is highly irrelevant to the subject matter of claims 28 and 97 – See Table 2 of Applicants' submission dated April 19, 2007) because it actually focuses of optimization of a protocol for PNA oligomer synthesis using t-boc/Z protected monomers, which comprise an acid-labile N-terminal amine protecting group. As such it is non-analogous art to the subject matter of claims 28 and 97 which are directed to the removal of a "*base-labile N-terminal amine protecting group*".

For these reasons, reliance on *Syngenta* to support a finding that the element/limitation of "*treating the solid support for a period of no more than about 1 to about 2 minutes with a deprotection reagent, under basic conditions, that deprotects the base-labile N-terminal amine protecting group*" is an obvious variation of the teachings of the references is incorrect.

In brief, Applicants maintain that no *prima facia* case for obviousness exists with respect to the subject matter of independent claims 28 and 97 (and claims dependent thereon). Reconsideration and withdrawal of the rejection of claims 28, 75-86 and 97-109 is therefore respectfully requested.

b) Claims 41, 87-93 and 95-96

Applicants again refer to their arguments submitted on April 19, 2007. In particular, Applicants again refer to tables 1 and 2 at pages 14-15. Applicants note in particular that Breipohl, Kovacs, Thomson and/or Koch fail to teach the element/limitation of a support wherein "*a final loading of the PNA dimer on the solid support is greater than or equal to 0.08 mmol per gram*".

In rebuttal the Office Action suggests that the references do teach this limitation. However, the references relied upon do no more than report an initial loading of the resin (i.e. the pre-synthesis loading). The references do not teach loading of the PNA dimers on the support (post synthesis of dimer) and Applicants' specification (See Example 1) demonstrates that initial loading is in no way representative of the loading as the synthesis progresses. Thus, the assertion that initial loading is representative of the loading of the PNA dimer on the resin is incorrect. Moreover, the rebuttal argument specifically takes notice that there is decomposition associated with the chemistry (OA at page 8). Accordingly, the present Office Action implicitly acknowledges that the 'initial' resin 'loading' will drop. This statement clearly weakens the Office's position and confirms Applicants'. In short, the present Office Action does nothing to contradict Applicants' assertion that the references fail to teach at least one element/limitation of independent claim 41.

Applicants further reiterate that Breipohl, Kovacs and Thomson are not relevant art to claims 41, 87-93 and 95-96 because they apply solely to methods wherein the N-terminal amine protecting group is base-labile. By comparison, independent claim 41 (and dependent claims 87-93 and 95-96) is directed to a method with requires "*treating the solid support with a deprotection reagent, under acidic conditions, that deprotects the acid-labile N-terminal amine*

protecting group." Although Koch teaches methods for deprotection of the acid-labile N-terminal amine protecting group, these methods are not applied to a solid support comprising an acid-forming cleavable linker. Moreover, because the synthetic protocols of Breipohl, Kovacs and Thomson are incompatible with the synthetic protocols taught by Koch, there is no basis to combine them, and there is no a reasonable expectation of success in combining them, to thereby achieve the subject matter of claims 41, 87-93 and 95-96.

For the reasons stated, it is respectfully submitted that no *prima facia* case for obviousness has been established by the Office. Reconsideration and withdrawal of the rejections of claims 41, 87-93 and 95-96 is therefore respectfully requested.

II Rejection over Seitz, Thomson and Koch

At page 12, claims 28, 75, 77, 97, 98 and 100 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Seitz (*Tetrahedron Letters*, **40:**4161-4164 (1999)), in view of Thomson and Koch. This rejection is respectfully traversed.

Applicants refer to and reiterate the arguments presented at pages 17-18 of their submission dated April 17, 2007.

Moreover, the deficiencies of Thomson and Koch with respect to independent claims 28 and 97 (and claims dependent thereon) have been discussed above. Seitz provides no protocol for synthesizing PNA oligomers comprising: "*a base-labile N-terminal amine protecting group*". The prophetic statement at page 4163 (sentence just above Scheme 4) is irrelevant since it provides no information whatsoever that would aid the ordinary practitioner in performing the synthesis of a PNA oligomer from PNA monomers comprising a "*base-labile N-terminal amine protecting group*". Accordingly, this statement does not cure the deficiencies of Thomson or Koch. For example, Seitz does not provide any teaching which would suggest that: "... *reaction time adjustments in the range of about 1 to about 2 minutes as [sic] a matter of routine experimentation*" of conditions used to remove "*a base-labile N-terminal amine protecting group*". (OA at page 13-14, bridging sentence).

For the reasons stated, it is respectfully submitted that no *prima facia* case for obviousness has been established by the Office. Reconsideration and withdrawal of the rejections of claims 28, 75, 77, 97, 98 and 100 is therefore respectfully requested.

Conclusion

It is respectfully submitted that the application is in condition for allowance. A notice of allowance is therefore respectfully requested. If any issues remain that can be resolved by phone, Applicants request that the Examiner contact the undersigned at 781-271-0008. All other correspondence pertaining to this matter should be directed to the address associated with Customer Number 23544.

Exhibits

Attached hereto are:

Exhibit D

Exhibit E

FEE AUTHORIZATION

Should any extension of time and/or fee be necessary for timely submission of this paper, such extension of time is hereby requested, and the Commissioner is hereby authorized to charge Applied Biosystems Deposit Account No. 01-2213 (order no. **BP0206US-CN1**). Any deficiency or overpayment should be charged or credited to this deposit account.

Respectfully submitted,

Date: Nov 19, 2007

Brian D. Gildea
Agent for Applicants
Reg. No. 39,995

Claims

1. A solid support composition comprising:
   a) an acid forming cleavable linker; and
   b) a PNA dimer, comprising an N-terminal base labile protecting group, cleavably linked to the solid support through the cleavable linker, wherein the loading of the PNA dimer on the solid support is greater than or equal to 0.08 mmol per gram.
2. The composition of claim 1, wherein the solid support is a sterically hindered solid support.
3. The composition of claim 2, wherein the sterically hindered solid support is selected from the group consisting of: Trityl chloride resin (Trityl-Cl), 2-Chlorotrityl chloride resin, DHPP, MBHA, 4-methyltrityl chloride resin, 4-methoxytrityl chloride resin, Hydroxy-(2-chlorophenyl)methyl-PS, Rink Acid Resin and NovaSyn TGT alcohol resin.
4. The composition of claim 1, wherein the solid support is selected from the group consisting of: PAL-PEG-PS™, NovaSyn TGA and Wang Resin.
5. The composition of claim 1 or 2, wherein the PNA dimer is linked to the cleavable linker by an ester bond.
6. The composition of claim 1 or 2, wherein the PNA dimer is formed from Fmoc(Bhoc) monomers.
7. The composition of claim 1 or 2, wherein the loading of the PNA dimer on the solid support is in the range from about 0.1 mmol per gram to about 1 mmol per gram, preferably from about 0.12 mmol per gram to about 0.35 mmol per gram.
8. The composition of claim 1 or 2 wherein the solid support is an array comprising two or more different support bound PNA dimers.
9. A library comprising at least two solid supports wherein said at least two solid supports each comprise:
   a) an acid forming cleavable linker; and
   b) a PNA dimer that: (i) is cleavably linked to the acid forming cleavable linker; and (ii) differs in nucleobase sequence from the

PNA dimer that is linked to any of the other of the at least two solid supports of the library.

10. The library of claim 9, wherein the library comprises at least sixteen solid supports, each support comprising a PNA dimer chosen from a set of at least sixteen possible PNA dimers wherein each PNA dimer of the set differs from all of the other PNA dimers of the set by at least one of at least four different nucleobases.

11. The library of claim 10, wherein each of the at least four different nucleobases is selected from the group consisting of: adenine, cytosine, guanine, thymine, uracil, 5-propynyl-uracil, 2-thio-5-propynyl-uracil, 5-methylcytosine, pseudoisocytosine, 2-thiouracil and 2-thiothymine, 2-aminopurine, N9-(2-amino-6-chloropurine), N9-(2,6-diaminopurine), hypoxanthine, N9-(7-deaza-guanine), N9-(7-deaza-8-aza-guanine) and N8-(7-deaza-8-aza-adenine).

12. The library of claim 9, wherein the solid support is a sterically hindered solid support.

13. The library of claim 12, wherein the sterically hindered solid support is selected from the group consisting of: Trityl chloride resin (Trityl-Cl), 2-Chlorotrityl chloride resin, DHPP, MBHA, 4-methyltrityl chloride resin, 4-methoxytrityl chloride resin, Hydroxy-(2-chlorophenyl)methyl-PS, Rink Acid Resin and NovaSyn TGT alcohol resin.

14. The library of claim 9, wherein the solid support is selected from the group consisting of: PAL-PEG-PS, NovaSyn TGA and Wang Resin.

15. The library of claim 9 or 12, wherein the PNA dimer is linked to the cleavable linker by an ester bond.

16. The library of claim 15, wherein the C-terminal subunit of the PNA dimer is linked to the cleavable linker.

17. The library of claim 12, wherein the PNA dimer is formed from Fmoc(Bhoc) protected PNA monomers.

18. The library of claim 9 or 12, wherein the PNA dimer is formed from t-boc/Z protected PNA monomers, Mmt/Bhoc protected PNA monomers or both Mmt/Bhoc protected PNA monomers and Fmoc(Bhoc)protected PNA monomers.

19. The library of claim 9 or 12, wherein the loading of the PNA dimer on at least one solid support of the library, preferably on at least one half of the solid supports of the library, more preferably on all of the solid supports of the library is greater than or equal to 0.08 mmol per gram.

20. The library of claim 19, wherein the loading of the PNA dimer on each solid support of the library is in the range from about 0.1 mmol per gram to about 1 mmol per gram, preferably from about 0.12 mmol per gram to about 0.35 mmol per gram.

21. The library of claim 9 or 12, wherein the library of supports is arranged to produce an array.

22. A method for forming a support bound PNA dimer, said method comprising:

a) coupling a first PNA monomer to a sterically hindered solid support comprising a sterically hindered acid forming cleavable linker wherein the PNA monomer comprises a N-terminal amine base labile protecting group;

b) optionally washing the solid support to remove excess first PNA monomer;

c) treating the solid support for a period of about 1 to about 2 minutes with a deprotection reagent that substantially removes the base labile N-terminal amine protecting group from the support bound first PNA monomer but that does not allow for more than 50 percent cyclization and elimination of the first PNA monomer from the support;

d) washing the solid support to remove the deprotection reagent; and

e) coupling a second PNA monomer to the N-terminal amine of the first PNA monomer as soon as is practical after performing steps (c) and (d).

23. The method of claim 22, wherein the first and second PNA monomers are Fmoc(Bhoc) PNA monomers comprising the same or a different nucleobase.

24. The method of claim 22, wherein the N-terminal base labile protecting group is Fmoc.

25. The method of claim 22, wherein the deprotection reagent is a solution containing from about 15 to about 25 percent piperidine in an organic solvent, preferably 20 percent piperidine in N,N'-dimethylformamide (DMF), or the deprotection reagent is a solution containing from about 0.2% to about 4% (v/v), preferably about 2% DBU in NMP.

26. The method of claim 22, wherein the sterically hindered solid support is selected from the group consisting of: Trityl chloride resin (Trityl-Cl), 2-Chlorotrityl chloride resin, DHPP, MBHA, 4-methyltrityl chloride resin, 4-

methoxytrityl chloride resin, Hydroxy-(2-chlorophenyl)methyl-PS, Rink Acid Resin and NovaSyn TGT alcohol resin.

27. The method of claim 22, wherein the final loading of the PNA dimer on the solid support is greater than or equal to 0.08 mmol per gram, preferably from about 0.1 mmol per gram to about 1 mmol per gram, more preferably from about 0.12 mmol per gram to about 0.35 mmol per gram.

28. A method for forming a support bound PNA dimer, said method comprising:

a) coupling a first PNA monomer to solid support comprising an acid forming cleavable linker wherein the PNA monomer comprises an acid labile N-terminal protecting group;

b) optionally washing the solid support to remove excess first PNA monomer;

c) treating the solid support with a deprotection reagent under acidic conditions that deprotect the acid labile N-terminal protecting group;

d) washing the solid support to remove the deprotection reagent; and

e) coupling a second PNA monomer to the N-terminal amine of the first PNA monomer,

wherein the final loading of the PNA dimer on the solid support is greater than or equal to 0.08 mmol per gram.

29. The method of claim 28, wherein the first and second PNA monomers are t-boc/Z protected PNA monomers or Mmt/Bhoc protected PNA monomers comprising the same or a different nucleobase, or the first PNA monomer is an Mmt/Bhoc protected PNA monomer and the second PNA monomer is an Fmoc/Bhoc protected PNA monomer.

30. The method of claim 23 or 28, wherein the nucleobase of the first and second PNA monomer is independently selected from the group consisting of: adenine, cytosine, guanine, thymine, uracil, 5-propynyl-uracil, 2-thio-5-propynyl-uracil, 5-methylcytosine, pseudoisocytosine, 2-thiouracil and 2-thiothymine, 2-aminopurine, N9-(2-amino-6-chloropurine), N9-(2,6-diaminopurine), hypoxanthine, N9-(7-deaza-guanine), N9-(7-deaza-8-aza-guanine) and N8-(7-deaza-8-aza-adenine).

31. The method of claim 28, wherein the first PNA monomer is an Mmt/Bhoc protected PNA monomer and the deprotection reagent is a solution containing from about 1 to about 5 percent (v/v) dichloroacetic acid in an

organic solvent, preferably the deprotection reagent is about 2 percent dichloroacetic acid in dichloromethane (DCM).

32. The method of claim 28, wherein the solid support is a sterically hindered solid support selected from the group consisting of: Trityl chloride resin (Trityl-Cl), 2-Chlorotrityl chloride resin, DHPP, MBHA, 4-methyltrityl chloride resin, 4-methoxytrityl chloride resin, Hydroxy-(2-chlorophenyl)methyl-PS, Rink Acid Resin and NovaSyn TGT alcohol resin; or the solid support is selected from the group consisting of: Fmoc-PAL-PEG-PS, NovaSyn TGA and Wang Resin.

33. The method of claim 28, wherein the final loading of the PNA dimer on the solid support is in the range from about 0.1 mmol per gram to about 1.2 mmol per gram, preferably from about 0.12 mmol per gram to about 0.35 mmol per gram.

34. A PNA C-terminal acid oligomer comprising a C-terminal PNA subunit and a fluorescent label or quencher.

35. The PNA oligomer of claim 34, wherein the fluorescent label is Dye 1 or Dye 2.

36. The PNA oligomer of claim 34, wherein the quencher moiety is dabcyl.

37. The PNA oligomer of claim 34, wherein the PNA oligomer is 10 or less, preferably from about 3 to about 8, more preferably from about 4 to about 6, more preferably 4 or 5 subunits in length.

38. The PNA oligomer of claim 34, wherein the label is linked to the N-terminal subunit or N-terminal amine of the PNA oligomer.

39. The PNA oligomer of claim 34, wherein the nucleobases of the oligomer are selected from the group consisting of: adenine, cytosine, guanine, thymine, uracil, 5-propynyl-uracil, 2-thio-5-propynyl-uracil, 5-methylcytosine, pseudoisocytosine, 2-thiouracil and 2-thiothymine, 2-aminopurine, N9-(2-amino-6-chloropurine), N9-(2,6-diaminopurine), hypoxanthine, N9-(7-deaza-guanine), N9-(7-deaza-8-aza-guanine) and N8-(7-deaza-8-aza-adenine).

40. A library of PNA C-terminal acid oligomers, each PNA oligomer of the library comprising:

a) a nucleobase sequence;

b) a C-terminal PNA subunit; and

c) a fluorescent label or quencher moiety;

wherein each PNA oligomer differs, either in label, nucleobase sequence, subunit length or polarity of nucleobase sequence, from each of the other PNA oligomers of the library.

41. The library of claim 40, wherein the nucleobases of each PNA oligomer are selected from the group consisting of: adenine, cytosine, guanine, thymine, uracil, 5-propynyl-uracil, 2-thio-5-propynyl-uracil, 5-methylcytosine, pseudoisocytosine, 2-thiouracil and 2-thiothymine, 2-aminopurine, N9-(2-amino-6-chloropurine), N9-(2,6-diaminopurine), hypoxanthine, N9-(7-deaza-guanine), N9-(7-deaza-8-aza-guanine) and N8-(7-deaza-8-aza-adenine).

42. The library of claim 40, wherein the fluorescent label or quencher of each PNA oligomer is linked to the N-terminal subunit, or N-terminal amine.

43. The library of claim 40, wherein each PNA oligomer of the library comprises the same number of PNA subunits.

44. The library of claim 40, wherein at least one of the PNA oligomers of the library comprise a different number of PNA subunits as compared to at least one other PNA oligomer of the library.

45. The library of claim 40, wherein each PNA oligomer of the library comprises from about 3 to about 8, preferably from about 4 to about 6, more preferably 4 or 5 PNA subunits.

46. The library of claim 40, wherein the library comprises at least two sets of PNA C-terminal acid oligomers wherein the PNA oligomers of each set differ from those of the other set primarily in the nature of a fluorescent label.

47. The library of claim 46, wherein the first set of PNA C-terminal acid oligomers is labeled with Dye1 and the second set of PNA C-terminal acid oligomers is labeled with Dye2.

Exhibit E

EPA/EPO/OEB
D-80298 München

☎ +49 89 2399-0
TX 523 656 epmu d
FAX +49 89 2399-4465

Europäisches Patentamt	European Patent Office	Office européen des brevets
Generaldirektion 2	Directorate General 2	Direction Générale 2

Telephone numbers: Branch at The Hague

Primary Examiner (substantive examination) +31 70 340-9487

Formalities Officer / Assistant (Formalities and other matters) +31 70 340-4259

Schnappauf, Georg
Geibelstrasse 6
81679 München
ALLEMAGNE

Application No.	Ref.	Date
03 755 797.2 - 1216	128-152	06.07.2007

Applicant
Applera Corporation

Communication pursuant to Article 96(2) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(1) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 78(2) and 83(2) and (4) EPC.

One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (Rule 36(1) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Article 96(3) EPC).

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SCHLEIFENBAUM, A
Primary Examiner
for the Examining Division

Enclosure(s): 6 page/s reasons (Form 2906)

Registered Letter
EPO Form 2001 07.02CSX

The examination is being carried out on the **following application documents**:

Description, Pages	1-31	as originally filed
Claims, Numbers	1-47	received on 08.08.2006 with letter of 08.2006
Drawings, Sheets	1-6	as originally filed

CITED DOCUMENTS

D1: SEITZ O: "Solid Phase Synthesis of Protected Peptide Nucleic Acids" TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 40, no. 22, 28 May 1999 (1999-05-28), pages 4161-4164, XP004164686 ISSN: 0040-4039

D2: HYRUP B ET AL: "PEPTIDE NUCLEIC ACIDS (PNA): SYNTHESIS, PROPERTIES AND POTENTIAL APPLICATIONS" BIOORGANIC & MEDICINAL CHEMISTRY, ELSEVIER SCIENCE LTD, GB, vol. 4, no. 1, 1996, pages 5-23, XP000602327 ISSN: 0968-0896

D3: KOVACS G., TIMAR Z., KUPIHAR Z., KELE Z., KOVACS L.: "Synthesis and analysis of peptide nucleic acid oligomers using Fmoc/acyl-protected monomers" J. CHEM. SOC., PERKIN TRANS. I, 23 April 2002 (2002-04-23), pages 1266-1270, XP002408946

D4: CAPASSO D ET AL: "Solid phase synthesis of DNA-3'-PNA chimeras by using Bhoc/Fmoc PNA monomers" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 57, no. 46, 12 November 2001 (2001-11-12), pages 9481-9486, XP004312081 ISSN: 0040-4020

D5: SEITZ O; KÖHLER O: "Convergent strategies for the attachment of fluorescing reporter groups to peptide nucleic acids in solution and on solid phase." CHEMISTRY, vol. 7, no. 18, 17 September 2001 (2001-09-17), pages 3911-3925, XP002408947

D6: WO 00/33084 A2 (SYNTRIX BIOCHIP INC [US]; ZEBALA JOHN A [US]) 8 June 2000 (2000-06-08)

D7: THOMSON S A ET AL: "FMOC MEDIATED SYNTHESIS OF PEPTIDE NUCLEIC ACIDS" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 51, no. 22, 29 May 1995 (1995-05-29), pages 6179-6194, XP002030024 ISSN: 0040-4020

UNITY (Article 82 EPC)

1. The present application comprises 4 inventions as listed below:
   Group I: Claims 1-8, 22-27

Solid support bound PNA dimers having a base labile N-terminal protection group and a method of production

Group II: Claims 9-21

Library comprising at least two solid supports comprising a PNA dimer cleavably attached via an acid forming linker.

Group III: Claims 28-33

Method for forming a solid support bound PNA dimer having an acid labile N-terminal protection group.

Group IV: Claims 34-47

Labelled PNA acids.

2. These inventions are not so linked as to form a single inventive concept for the following reasons:

3. The inventions solve the following problems:

Group I: Educt for base labile N-terminal protection group based solid phase PNA-synthesis of PNA C-terminal acids.

Group II: Provision of PNA-dimers linked to a solid support for PNA synthesis.

Group III: Preparation of an educt with an acid labile N-terminal protection group suitable for solid phase PNA-synthesis of PNA C-terminal acids.

Group IV: PNA C-terminal acids for optical detection.

4. The solutions provided by the inventions are:

Group I: PNA dimer bound to solid support and carrying a base labile N-terminal protection group.

Group II: PNA-dimer library.

Group III: Subsequent coupling of two PNA monomers, where the first residue carries an acid labile N-terminal protection group.

Group IV: PNA C-terminal acids with fluorophores or quenchers.

5. The common feature of group I, group II, group III and group IV are PNA C-terminal acids. However, such compounds are known in the art (see D1, compound 12; D2, compound 34) and therefore, cannot be seen as special technical feature.

6. A closer common feature of group I, group II and group III may be seen in PNA-dimers linked via an acid forming cleavable linker to a solid support. The document D1 provides the solid phase synthesis of a PNA C-terminal acid (see D1, compound 12). An isolated intermediate is a PNA dimer linked via an acid forming cleavable linker to a solid support (HYCRON resin). Therefore, also the second technical feature shared by group I, group II and III cannot be considered as linking these inventions in the sense of a special technical feature (Rule 30 EPC).

7. No closer relation between the inventions could be defined

8. Therefore, the present application addresses four different problems and provides four different solutions which are not linked by a special technical feature in the sense of Rule 30 EPC. Consequently, the application does not comply with the requirements of Article 82 EPC and comprises the four inventions as listed above.

9. As the applicant has not had a search report drawn up on the other inventions (Rule 46 EPC), the application will be prosecuted on the basis of the invention in respect of which a search has already been carried out, in other words the invention first mentioned in the claims. The applicant should therefore limit the application to the invention searched and excise those parts of the application relating to the other inventions.

10. The subject-matter to be excised may be made the subject of one or more divisional applications. The divisional applications must be filed directly at the European Patent Office in Munich or its branch at The Hague and in the language of the proceedings relating to the present application, cf. Article 76(1) and Rule 4 EPC. The time limit for filing divisional applications (Rule 25(1) EPC) must be observed.

CLARITY (Article 84 EPC)

11. The application does not meet the requirements of Article 84 EPC since the subject matter of claims 3, 4 and 26 is in contradiction to the subject-matter claimed by their respective independent claims 1 and 22. These independent claims refer to resins comprising acid forming cleavable linkers. However, the resins specified in claims 3, 4 and 26 also comprise amide forming cleavable linkers, in particular the resins MBHA and PAL-PEG-PS.

12. As the main inventions must be seen in the provision of educts for PNA C-terminal *acid* synthesis based on base labile protection groups, the search was based on the subject-matter of the independent claims, but not on the additional subject-matter introduced by the dependent claims 3, 4, 13, 14 and 26 (that is PNA C-terminal *amides*).

13. Further, the use of trademarks and abbreviations must be omitted since they do not have a precise meaning as they are not internationally accepted as standard descriptive terms, thereby rendering the definition of the subject matter of the claims unclear (Article 84 EPC; see the Guidelines, C-III, 4.5b).

14. Expressions of the type "cleavable linker" are not clear as virtually any chemical moiety may be seen as a "cleavable" linker (Article 84 EPC).

15. The term "sterically hindered solid support" is not clearly defined in the claims and therefore render them unclear (Article 84 EPC).

16. The term "about" used in claims 7, 22, 25 and 27 is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject matter of said claim/s unclear (Article 84 EPC).

NOVELTY & INVENTIVE STEP (Articles 54 and 56 EPC)

17. The cited documents disclose PNA oligomers. However, as each oligomer is successively built on solid support, the coupled monomer, dimer, trimer etc. are isolated intermediates and must be seen to be implicitly disclosed. Therefore, the subject matter of claim 1 is not new (Article 54 EPC).

18. Further, the present application does not meet the requirements of Article 52(1) EPC, because the subject matter of claim 1, 2, 4-7 is not new in the sense of Article 54(1) and (2) EPC.

19. The document D3 discloses (the references in parentheses applying to this document):

a solid support composition comprising an acid forming cleavable linker (Wang resin) and a PNA dimer (intermediate), comprising an N-terminal base labile protecting

group (Fmoc), cleavably linked to the solid support through the cleavable linker (also comprising a lysine, see compounds 5 and 8), wherein the loading of the PNA dimer on the solid support is greater than or equal to 0.08 mmol per gram (initial loading 0.5 mmol/g; coupling yields >94% => >0.44 mmol/g dimer).

Similar compositions are disclosed in document D4 [see D4, compound 8; this document anticipates novelty of claim 6 as Fmoc(Bhoc) monomers are used in synthesis] and D5 (see D5, Scheme 5, 9).

20. The subject matter of claim 1, 2, 4-6 is therefore not new (Article 54(1) and (2) EPC).

21. Even if the subject matter of claims 1,2 4-6 could be rendered novel, it would be obvious from the cited prior art, and therefore, not include an inventive step (Article 56 EPC).

22. The subject matter of claim 3 appears to be novel (Article 54 EPC), however, does not include an inventive step (Article 56 EPC). Its subject matter consists in the selection of solid supports well known to the man skilled in the art. Such a selection can only be regarded as inventive, if the solid support presents unexpected effects or properties in relation to the rest of the range. However, no such effects or properties are indicated in the application. Hence no inventive step is present in the subject matter of claim 3 (Articles 52(1) and 56 EPC).

23. The subject matter of claim 8 appears to be novel (Article 54 EPC), however, it does not involve an inventive step in the sense of Article 56 EPC. The subject-matter is defined by the form of the solid support. However, arrays of PNA dimers are known from document D6 (see D6, Example 6). These arrays are PNA modified on an amino group. Document D5 (see D5, Scheme 9, in particular steps a-c) provides a method to modify such solid supports with PNAs linked to the solid support via an acid forming cleavable linker. The combinations of the teaching of both documents leads the skilled man to the subject matter found in claim 8 of the present application without the need for inventive skills. Consequently, the subject matter of claim 8 is not inventive (Article 56 EPC).

24. The subject matter of claims 22-27 is novel and inventive as the prior art does not

teach to use deprotection steps of 1 to 2 minutes for PNAs coupled to a solid support via an acid forming cleavable linker.

FINISHING REMARKS

25. The applicant is invited to file new claims which take account of the above comments.

26. Amendments should be made by filing replacement pages. Unnecessary recasting of the description should be avoided. An amended abstract is not required. The applicant should also take account of the requirements of Rule 36(1) EPC. If handwritten amendments are submitted, they should be clearly legible for the printer. According to the decision of the President of the EPO under Rule 35(2) EPC (OJ EPO 12/2001, 563) one set of the amended documents of the European patent application shall be provided.

27. In order to facilitate the examination of the conformity of the amended application with the requirements of Article 123(2) EPC, the applicant should clearly identify the amendments carried out, irrespective of whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see Guidelines E-II, 1).

28. If the applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.

29. When filing amended claims the applicant should at the same time bring the description into conformity with the amended claims. Care should be taken during revision, especially of the introductory portion and any statements of problem or advantage, not to add subject matter which extends beyond the content of the application as originally filed (Article 123(2) EPC).